

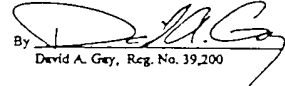


PATENT
Our Docket: P-IX 1655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:)
Kauffman and Ballivet) Group Art Unit: 1803
Serial No.: 08/464,141) Examiner: T. Wai
Filed: June 5, 1995)
For: PROCESS FOR OBTAINING)
DNA, RNA, PEPTIDES,)
POLYPEPTIDES, OR PROTEIN,)
BY RECOMBINANT DNA)
TECHNIQUE)

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Patents, Washington, D.C. 20231, on
February 5, 1998.

By 
David A. Grey, Reg. No. 39,200

Assistant Commissioner of Patents
Washington, D.C. 20231

February 5, 1998
Date of Signature

Sir:

RESPONSE TO OFFICE ACTION

Responsive to the Office Action mailed August 5, 1997,
entry of the amendments and consideration of following remarks is
respectfully requested.

AMENDMENTS

Please cancel claim 67.

Please amend the claims as follows:

1. (Twice amended) A process for the production of a
peptide, polypeptide, or protein having a predetermined property,
comprising the steps of:

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producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing ~~the~~ host cells [containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences];

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

2. (Twice amended) A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences[,];

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introducing the population of at least partially stochastic polynucleotide sequences [thus obtained] into host cells to produce transformed host cells;

h¹
cultivating the transformed host cells [containing the population of at least partially stochastic polynucleotide sequences so as to clone the stochastic polynucleotide sequences and lead to the production of] to produce peptides, polypeptides, or proteins expressed by at least some of the [these] stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said [clones of] transformed host cells to identify [those] clones producing the peptide, polypeptide, or protein having the predetermined property;

isolating the clones so identified[,] and

growing the isolated clones in a manner so as to produce the peptide, polypeptide, or protein having the predetermined property.

Please add the following new claims:

2-88. (New) A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

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producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

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forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.--

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4
--~~63~~. (New) A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones

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producing the peptide, polypeptide, or protein having
the predetermined property;

contacting the peptide, polypeptide, or protein
with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or
protein bound at each concentration of ligand.--

2
1) ~~4~~⁵ (New) The process according to claim ~~3~~³ or
claim ~~4~~⁵, wherein more than one ligand is detected or titrated.--

~~6~~⁶ (New) A method of identifying a peptide,
polypeptide or protein having a predetermined property,
comprising:

- (a) producing a population of peptides,
polypeptides or proteins encoded by
stochastic polynucleotide sequences;
- (b) screening said population of peptides,
polypeptides or proteins for said
predetermined property under conditions which
allow detection of one or more peptides,
polypeptides or proteins having said
predetermined property.--

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⁷
~~7~~. (New) The method of claim ⁶~~7~~, wherein step
(a) further comprises synthesizing a population of stochastic
polynucleotide sequences and translating said population of
stochastic polynucleotide sequences to produce said population of
peptides, polypeptides or proteins.--

⁸
~~8~~. (New) The method of claim ⁶~~7~~, wherein step
(a) further comprises synthesizing a population of at least
partially stochastic polynucleotide sequences and translating
said population of stochastic polynucleotide sequences to produce
said population of peptides, polypeptides or proteins.--

⁹
~~9~~. (New) The method of claim ⁷~~7~~ or ⁸~~8~~, further
comprising amplification of said population of stochastic
polynucleotide sequences.--

¹⁰
~~10~~. (New) The method of claim ⁶~~7~~, wherein step
(a) further comprises synthesizing a population of stochastic
polynucleotide sequences and expressing said population of
stochastic polynucleotide sequences to produce said population of
peptides, polypeptides or proteins.--

¹¹
~~11~~. (New) The method of claim ⁶~~7~~, wherein step
(a) further comprises synthesizing a population of at least
partially stochastic polynucleotide sequences and expressing said
population of stochastic polynucleotide sequences to produce said
population of peptides, polypeptides or proteins.--

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¹²
~~--27.~~ (New) The method of claim ⁶~~21~~, further comprising isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property.--

¹³
~~--28.~~ (New) The method of claim ⁶~~21~~, wherein said predetermined property comprises binding or chemical catalysis.--

¹⁴
~~--29.~~ (New) The method of claim ¹³~~28~~, further comprising improving said predetermined property by in vitro or in vivo mutagenesis.--

¹⁵
~~--30.~~ (New) The method of claim ¹³~~28~~, wherein said binding further comprises modification of a biological or chemical property of a compound bound by said peptide, polypeptide or protein.--

¹⁶
~~--31.~~ (New) The method of claim ¹⁵~~30~~, wherein said modification of said biological or chemical property of said compound further comprises stimulating or inhibiting at least one biological function of said compound.--

¹⁷
~~--32.~~ (New) A method of producing a peptide, polypeptide or protein having a predetermined property, comprising:

- (a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

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(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property;

D2

(c) isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property; and

(d) producing said peptide polypeptide or protein.--

~~18~~
~~--22--~~

(New) The method of claim ~~17~~¹⁷, wherein step (a) further comprises synthesizing a population of stochastic polynucleotide sequences and translating said population of stochastic polynucleotide sequences to produce said population of peptides, polypeptides or proteins.--

~~19~~
~~--24--~~

(New) The method of claim ~~17~~¹⁷, wherein step (a) further comprises synthesizing a population of at least partially stochastic polynucleotide sequences and translating said population of stochastic polynucleotide sequences to produce said population of peptides, polypeptides or proteins.--

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²⁰
~~--20.~~ (New) The method of claim ¹⁸ ~~18~~ or ¹⁹ ~~19~~, further comprising amplification of said population of stochastic polynucleotide sequences.--

²¹
~~--21.~~ (New) The method of claim ¹⁷ ~~17~~, wherein step (a) further comprises synthesizing a population of stochastic polynucleotide sequences and expressing said population of stochastic polynucleotide sequences to produce said population of peptides, polypeptides or proteins.--

B2 ²²
~~--22.~~ (New) The method of claim ¹⁷ ~~17~~, wherein step (a) further comprises synthesizing a population of at least partially stochastic polynucleotide sequences and expressing said population of stochastic polynucleotide sequences to produce said population of peptides, polypeptides or proteins.--

²³
~~--23.~~ (New) The method of claim ¹⁷ ~~17~~, further comprising isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property.--

²⁴
~~--24.~~ (New) The method of claim ¹⁷ ~~17~~, wherein said producing in step (d) further comprises chemical synthesis or recombinant expression.--

²⁵
~~--25.~~ (New) The method of claim ¹⁷ ~~17~~, wherein said predetermined property comprises binding or chemical catalysis.--

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²⁶
~~--24.~~ (New) The method of claim ²⁵~~20~~, further
comprising improving said predetermined property by *in vitro* or
in vivo mutagenesis.--

²⁷
~~--22.~~ (New) The method of claim ²⁵~~20~~, wherein said
binding further comprises modification of a biological or
chemical property of a compound bound by said peptide,
polypeptide or protein.--

2
²⁸
~~--23.~~ (New) The method of claim ²⁵~~20~~, wherein said
modification of said biological or chemical property of said
compound further comprises stimulating or inhibiting at least one
biological function of said compound.--

²⁹
~~--21.~~ (New) A method of producing a stochastic
polynucleotide population, comprising synthesizing stochastic
polynucleotide sequences.--

³⁰
~~--25.~~ (New) The method of claim ²⁹~~24~~, further
comprising chemical synthesis.--

³¹
~~--26.~~ (New) The method of claim ²⁹~~24~~, further
comprising enzymatic synthesis.--

³²
~~--27.~~ (New) The method of claim ²⁹~~24~~, further
comprising joining oligonucleotide building blocks.--

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³³
~~--98.~~ (New) The method of claim ²⁹~~27~~, further comprising cleaving said population of stochastic polynucleotide sequences.--

³⁴
~~--99.~~ (New) The method of claim ³³~~31~~, further comprising ligating said cleaved population of stochastic polynucleotide sequences to produce a new ensemble of stochastic polynucleotide sequences.--

³⁵
~~--100.~~ (New) A method of producing a desired compound, comprising combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react, and incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time so as to allow the catalysis of said desired compound.--

³⁶
~~--101.~~ (New) A method of identifying a population of peptides, polypeptides or proteins which catalyze a sequence of chemical reactions, comprising:

- (a) combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react;

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(b) incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time to allow the catalysis of said sequence of chemical reactions, and

D²

(c) determining the presence or absence of a compound produced by said sequence of chemical reactions, the presence of said compound indicating that said population of peptides, polypeptides or proteins can catalyze said sequence of chemical reactions.--

³⁷
~~37~~ (New) The method of claim ³⁶~~37~~, further comprising the steps:

(d) dividing the population of peptides, polypeptides or proteins that can catalyze said sequence of chemical reactions into two or more subpopulations;

(e) repeating steps (a) through (c), and

(f) determining the subpopulation which catalyzes the sequence of chemical reactions.--

³⁸
~~38~~ (New) The method of claim ³⁷~~38~~, wherein steps (d) through (f) are repeated one or more times.--



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REMARKS

Claims 1, 2, and 67 are pending. Claim 67 has been canceled above and new claims 68-103 have been added. Therefore, the claims now under consideration are claims 1, 2 and 68-103. Support for the amendments can be found throughout the specification. Specifically, support for the amendment to claim 1 to recite a step for introducing the vectors can be found, for example, on page 9, lines 3 to 10. New claim 68 recites the subject matter of claim 1 and canceled claim 67. New claim 69 recites the subject matter of claim 2 and canceled claim 67. New claim 70 has support in the specification, for example, on page 5, lines 22 to 24.

New claims 71-93 and 101-103 are all directed to methods of identifying or producing peptides, polypeptides or proteins having predetermined properties. Claims 94-99 are directed to methods of producing the polynucleotide populations which can be used for making the peptides, polypeptides or proteins and claim 100 is directed to a use of a predetermined property of the peptides, polypeptides or proteins.

Support for independent claims 71-82 and, 94 and their dependents can be found, for example, throughout the specification; in the currently pending claims; in claim 6 as originally filed; on page 5, lines 1-24; on page 17, lines 9-14; and on page 34, lines 21-22. Further support for dependent claims 79 and 91 can be found, for example, on page 17, lines 4-8; page 20, lines 14-15; and page 26, lines 12-15. Further

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support for dependent claim 98 can be found, for example, on page 4, lines 15-20; and page 16, lines 10-18. Support for independent claims 100 and 101 and their dependents, as well as for dependent claims 78 and 90, can be found, for example, as described above and on pages 29-37. Therefore, the amendments do not raise an issue of new matter and entry thereof is respectfully requested.

The present invention provides methods for producing peptides, polypeptides, or proteins having a predetermined property and also methods for the detection or titration of a ligand. The methods consist of synthesizing diverse populations of stochastic polynucleotide sequences and screening the population for those having the predetermined property. The methods rely on synthesizing a sufficiently large population, or a population with sufficient diversity so as to contain a likely probability that the sequence exhibiting, or encoding, the predetermined property is represented within the stochastic population. Identification and isolation of the peptide, polypeptide or protein can be achieved by screening the diverse population using a variety of methods known to those skilled in the art. The claimed methods utilizing large populations of stochastic sequences provide advantages over previous methods in that no prior information regarding the sequence is required. Instead, sequences encoding binding properties, for example, to a ligand can be identified by screening the population with a detectable ligand. Applicants traverse all grounds for rejecting the claims in the Office Action for the reasons which follow.

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REJECTION UNDER 35 U.S.C. § 101

Claim 67 stands rejected under 35 U.S.C. § 101, as allegedly containing non-statutory subject matter. In this regard, the Examiner states that the "use of a product" claim is non-statutory subject matter. Applicants have reworded original claim 67 as new claims 68 and 69. As stated previously, new claims 68 and 69 recite the steps for producing stochastic peptides, polypeptides or proteins encompassed by claims 1 and 2 and additionally recite required steps for detecting and/or titrating a ligand. Therefore, the new claims are believed to recite statutory subject matter. Accordingly, Applicants respectfully request the Examiner remove the rejection under 35 U.S.C. § 101.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2 and 67 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office Action states that claim 1 and its dependent are indefinite for allegedly failing to recite positive steps. In this regard, the Examiner suggests that the step of "introducing the vectors into host cells" should be recited as a step which leads to the formation of a library. Applicants contend that such a step is inherent in the claims as filed and is sufficiently clear to enable those skilled in the art to practice the invention as claimed. Nevertheless, to expedite prosecution of these claims, Applicants have amended claim 1 and added new claims 68 and 69 to recite this step.

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The Office Action also states that claim 1 and dependent claim 67 are indefinite because the meaning of "using the isolated sequence" is allegedly not clear. Applicants submit that it would have been routine for one skilled in the art to produce the peptide, polypeptide or protein using the information within the isolated sequence. For example, the isolated sequence need only be inserted into an appropriate expression system to produce the peptide, polypeptide or protein. Additionally, the peptide, polypeptide or protein can be chemically synthesized using the isolated sequence as a template. Thus, Applicants believe that the meaning of the phrase "using the isolated sequence" is sufficiently clear and concise to allow those skilled in the art to practice the invention as claimed.

The Office Action states that in claims 1, 2 and dependent claim 67, the meaning of the phrase "predetermined property" is not clear. Applicants believe that the term is sufficiently defined in the specification so as to allow one skilled in the art to practice the invention as claimed. The practitioner determines which property is screened for in the claimed methods and, therefore, which property is to be identified. For example, if the practitioner desires the identification of a peptide, polypeptide, or protein having a binding property to an antibody, receptor, or receptor ligand of interest, for example, then the practitioner will use these molecules to identify a peptide, polypeptide or protein encoded by a stochastically generated polynucleotide sequence which exhibits the predetermined binding property to the selected molecule.

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Alternatively, one can screen and identify peptides, polypeptides and proteins having properties such as exhibiting antigenic epitopes to a pathogen or being capable of modifying transcription, replication or stability of DNA, for example. Additionally, the property exhibited by the identified peptide, polypeptide or protein can be improved by mutagenesis and further selected, for example, to identify variants which exhibit enhanced characteristics compared to the initial predetermined property. Additional properties which can be used as a means to screen and identify peptides, polypeptides or proteins which exhibit the selected property include, for example, the catalysis of a chemical reaction and the production of reflexively autocatalytic populations. Such examples, as well as others, can be found described throughout the specification.

Thus, in light of the teachings within the specification, the use of the term "predetermined" references the property of the peptide, polypeptide or protein that is screened for and therefore the property that is determined beforehand. In light of these teachings, Applicants assert that the objected term is sufficiently clear to enable one skilled in the art to practice the invention as claimed.

The Office Action also states that in claim 2 and dependent claim 67, the meaning of the phrase "at least partially stochastic polynucleotide sequences" is not clear. Applicants believe that the phrase is sufficiently defined and clear in the specification so as to allow one skilled in the art to practice the invention as claimed. For example, included within the

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definition of the term "stochastic" is random. As is known to those skilled in the art, this term means that the claimed populations are random and as such are diverse. Diversity is an inherent outcome of the random polymerization of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined or specific sequence.

In light of the teachings within the specification, the phrase "at least partially stochastic polynucleotide sequences" is intended to include sequences which are random, as described above. In addition, the phrase can include a sequence, part of which is stochastically generated, and part of which is not stochastically generated. The part that is not stochastically generated can be a known or unknown sequence. The phrase can additionally include a sequence that contains a biased amount of any one or all of the four nucleotide triphosphates or other building blocks which comprise the polynucleotide sequence. Thus, the meaning of the term "at least partially stochastic synthetic polynucleotide sequences" would have been clear to one skilled in the art.

In light of the above remarks, Applicants believe that the claims are sufficiently clear so as to allow one skilled in the art to practice the invention as claimed. Applicants therefore, respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

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DOUBLE-PATENTING REJECTION

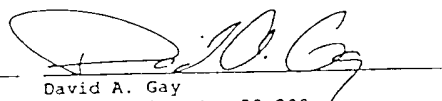
The provisional rejection of claims 1, 2 and 67 for same invention type double-patenting over claims 1, 2 and 67 of copending application Serial No. 08/468,468, is respectfully traversed. Applicants respectfully request that this rejection be held in abeyance until such time as there is an indication of allowable subject matter.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call Cathryn Campbell or the undersigned agent

Respectfully submitted,

Date: February 5, 1999


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